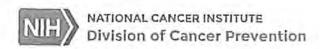
ASSAIA BENGE



### Grant R01CA155638

## Phosphodiesterase 5: A Novel Target and Inhibitor for Breast Cancer Chemopreventi

Organization:	 
Gary A Piazza University Of South Alabama	
Fiscal Year:	
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# Research Group and Program Tags:

Nonsteroidal anti-inflammatory drugs (NSAIDs) strongly inhibit tumorigenesis in experimental animal models, but toxicity from cyclooxygenase (COX) inhibition limits their use in humans for cancer chemoprevention. Previous studies have concluded that a COX-independent mechanism is responsible their antineoplastic activities, which suggests that it may be feasible to develop safer and more efficacious drugs by targeting such mechanisms. We have found that the tumor cell growth inhibitory and apoptosis inducing properties of certain NSAIDs such as sulindac sulfide (SS) are closely associated with inhibition of the cGMP-specific phosphodiesterase, PDE5. SS can selectively inhibit PDE5 to increase intracellular cGMP levels and activate protein kinase G to phosphorylate 2-catenin, thereby inducing its degradation to suppress the transcription of key apoptosis regulatory proteins such as survivin. Recently, we have shown that siRNA knockdown of PDE5 can selectively induce apoptosis of tumor cells as does SS. The proposed studies will focus on breast cancer chemoprevention since PDE5 appears to be the predominant cGMP degrading isozyme in breast tumor cells that is also expressed in adenocarcinomas from breast cancer patients. We hypothesize that PDE5 plays an important role in breast tumorigenesis that can be targeted to develop safe and efficacious drugs for breast cancer chemoprevention. In support of this hypothesis, we have synthesized a series of novel tadalafil derivatives that potently and selectively inhibit the growth and induce apoptosis of breast tumor cells. To further test this hypothesis, Aim 1 will determine the

importance of PDE5 and cGMP signaling for the anticancer activity of novel tadalafil derivatives and will evaluate PDE5 expression in human breast tumors; Aim 2 will synthesize and evaluate novel tadalafil derivatives for in vitro anticancer activity and will identify candidates with optimal pharmacological properties for in vivo efficacy testing; and Aim 3 will evaluate chemopreventive efficacy and safety of an optimal tadalafil derivative and will confirm mechanism of action in vivo. The goals of these studies are to validate PDE5 as an anticancer target, determine its potential role in cancer, and identify a safe and effective tadalafil derivative for preclinical drug development.

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Case 3:16-md-02691-RS Document 845-10 Filed 01/11/19 Page 3 of 3

Grant R01CA155638 | Division of Cancer Prevention

Page 3 of 3

Supportive and Palliative Care

#### **General Information**

Cancer Prevention, Specific Cancers, Clinical Trials

Cancer Screening Topics For People Who Have No Symptoms

Managing The Side Effects of Cancer and Its Treatment

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